

Brains for Dementia Research: Evolution in a Longitudinal Brain Donation Cohort to Maximize Current and Future Value

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Abstract. Brain banking has a long and distinguished past, contributing greatly to our understanding of human neurological and psychiatric conditions. Brain banks have been operationally diverse, collecting primarily end stage disease, with variable quality clinical data available, yet it is now recognized the most informative brain donations are from those in longitudinally studied cohorts. The Brains for Dementia Research (BDR) cohort and program was for planned brain donation across five UK brain banks and one donation point, with standardized operating procedures, following longitudinal clinical and psychometric assessments for people with no cognitive impairment as well as those with dementia. Lay representatives with experience of dementia were involved from inception of BDR and 74.5% of all enquiries about participation came through routes that were directly attributable to or influenced by lay representatives. Ten years after inception, this ongoing project has received over 700 brain donations from the recruited cohort of 3,276 potential brain donors. At cohort census for this paper, 72.2% of the living cohort have no cognitive impairment by assessment, whereas only 28.3% of the donated cohort were without cognitive impairment. It is important that brain banks are agile and reflect the changing needs of the research community, given that 'big data', readiness cohorts, and GWAS demand large sample numbers of highly characterized individuals to facilitate new approaches and understanding of pathological processes in dementia.

Keywords: Brain donation, cohort, control, dementia, research tissue bank

INTRODUCTION

Banking of brain tissue for diagnosis and research has a long history [1], traceable in the field of dementia to the work of Alois Alzheimer in the early 1900s [2]. There has, however, been a worldwide reduction in postmortem examinations with a follow-on reduction in banked postmortem brain tissue, especially from individuals with no history of brain disease. Most brain donations were *ad hoc*, commonly very

end stage disease, with variable clinical information mostly from General Practitioner records and often lacking a formal clinical diagnosis. These aspects and the response of brain banks, researchers, funders, and other stakeholders have been reviewed elsewhere [3, 4]. A search of Pubmed using the terms "brain banking" or "brain bank" identified 92 relevant articles, the first published in 1988 with a series of articles published in 1993 including the following examples [5, 6]. A very recent edition of the *Handbook of Clinical Neurology* also contains a series of relevant articles [7]. Significant challenges exist to collecting autopsies from potentially informative cohorts, such as the Alzheimer's Disease Imaging Initiative (ADNI), and

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are mainly resource-related [8, 9]. A recent publication from the UK has used brain donation from a longitudinal assessment cohort to identify a potential early diagnostic test [10].

In the UK, patient groups had been lobbying since the early 2000s to be able to donate their own brains, and those of family members with dementia, for research. They recognized the importance of human tissue being available alongside animal and cellular models. These factors, combined with the shortage of control brain tissue, led to BDR (brainsfor-dementiaresearch.org.uk) being established in 2008, through funding from the Alzheimer's Research UK (ARUK) and Alzheimer's Society (AS).

ARUK and AS recognized the UK brain banks, while excellent, were operationally diverse, which meant interpretation of results from larger scale studies requiring tissue from multiple banks carried problems. The funders' aim (and hence the aim for BDR) was for dementia brain banks to operate as a cohesive unit, with standardized procedures enabling the overall tissue collection to be of the highest ethical and scientific standards to facilitate and increase the best research. Thus, the BDR program was and is that of planned brain donation following longitudinal clinical and psychometric data collection from individuals with dementia and those with no cognitive impairment from a network of recruitment centers and brain banks. This approach accords with the results of a recent survey of brain banks where standardization, collaboration, and premortem data collection were highlighted [11].

Emergence of 'big data', readiness cohorts, and techniques requiring large sample numbers (e.g., genome wide association (GWAS), epigenetics), have been the drivers for evolution of the BDR cohort protocol while maintaining cohort agility. This maximizes the usefulness of tissue and data collected and ensures the tissue and data collected will continue to be a highly valuable resource in the field of dementia research for many years to come. This paper describes the cohort set-up, clinical data, and psychometric assessment measures collected and gives details of the cohort (both the living and brain donations to census date). Tissue and data are available for researchers and access information is given. How the BDR cohort fits with other study cohorts with an option for brain donation is discussed along with the position of BDR in relation to the changing landscape of dementia cohorts and initiatives in the UK and Europe to accelerate dementia understanding and drug discovery.

MATERIALS AND METHODS

Ethical and legal framework

BDR was established as a Research Tissue Bank following application and approval by the National Research Ethics Service. This encompassed recruitment of participants without dementia via a variety of means, provided informed consent for regular assessment and their consent to donate their brain for research upon death. All brain samples were stored in established brain banks that were working under license from the UK Human Tissue Authority. Subsequent adoption by the Clinical Research Network (funded by the UK National Institute of Health Research NIHR), and service support costs from the UK Medical Research Council (MRC) through the MRC UK Brain Bank Network, further facilitated assessment of participants and brain tissue characterization for the cohort.

The BDR Blood Biobank is covered by approval 13/SC/0516 granted by the Oxford C Committee of the National Research Ethics Service.

Cohort set up and recruitment

Following a tendering process which included the funding charities, lay representatives and an international review panel, BDR was established. The first funding phase was 2008 to 2013, the second from 2013 to 2018 and funding is agreed for a third phase 2018 to 2021. Funding charity staff and lay representatives were included in the configuring of the original project and have been involved in every area of the project subsequently [12]. BDR is a network of 6 dementia research centers (based at the universities of King's College London, Bristol, Manchester, Oxford, Cardiff and Newcastle) and the associated university brain banks handling the donations (Cardiff brain donations were banked in London). Each bank was well-established before BDR and each is a member of the MRC UK Brain Bank Network that was formed after BDR. The first director of the MRC network, Prof James Ironside, and second Director, Prof Seth Love, worked closely with the BDR Director to ensure close alignment of all protocols. Coordination and overall management of BDR was based at King's College London but has recently moved to Newcastle under the new Director, Prof Alan Thomas.

Participants were recruited with support from ARUK and AS (both press teams and lay representatives), using national and local press, TV

and radio coverage, articles in charity newsletters, national magazines with an older following, BDR posters, leaflets, memory clinics, talks at carer/support groups, Women's Institute, University of the Third Age. BDR has a dedicated website with links from the funding charities, MRC and Human Tissue Authority websites.

Participants with capacity were asked to identify and appoint a nominated representative (within the consent form) to facilitate brain donation when the time came, and also identify someone who knew them well enough to assist as a study partner in the clinical assessments. In the case of participants who lacked capacity to make decisions, a consultee (usually a family member) was appointed to assist the team in deciding if the participant would have wished to take part in the project and register the participant. After death, the consultee or suitable family member would then provide consent for autopsy and brain donation. The consultee was the study partner or authorized others (such as carers) to act as study partners. Nominated representatives/consultees and study partners could be the same person. Should cognitive impairment of a control participant decline such that capacity to give ongoing consent was fluctuating or lacking, the nominated representative and study partner were ideally placed to be approached about acting as a consultee with respect to BDR.

Exclusion criteria to undergo assessments included: 1) factors precluding brain donation (e.g. brain injury/trauma, major stroke), 2) being below age 65 for healthy controls (except where they were spouses/partners of participants with dementia), 3) having insufficient English language skills for completing assessments, and 4) being geographically too remote from an assessment center.

Assessments

All assessments were conducted by a trained psychologist or research nurse. Baseline assessments were conducted face to face (in the participant's place of residence or a BDR center), follow up assessments were usually face to face but telephone interviews were also used for some healthy control participants [13]. Follow up interviews were annual for participants with cognitive impairment, and between 1 to 5 years (depending on age) for cognitively healthy participants. To maximize the ability of collected data to be combinable with data from other cohorts, widely used assessment measures were adopted and the BDR assessment

Table 1

Operational criteria to generate cognitive status at assessment			
Measure (In order of preference)	Case	MCI	Control
CDR Global score (Range 0–3)	≥1	0.5	0
MMSE (Range 0–30)	≤23	24–26	27–30
MoCA (Range 0–30)	≤17	18–26	≥27
MoCA Blind (Range 0–22)	≤13	14–17	≥18
Global Deterioration Scale (1–7)	≥4	3	≤2
TICS-M (Range 0–40)	≤22	Inconclusive	≥23

Values indicate threshold scores or ranges in each category. MCI, mild cognitive impairment; CDR, Clinical Dementia Rating; MMSE, Mini-Mental Status Examination; MoCA, Montreal Cognitive Assessment; TICS-M, Telephone Interview of Cognitive Status-Modified. For details see text.

protocol taken from that used for the European Union FP6 program AddNeuroMed [14]. Assessment measures included socioeconomic data and case history [11], the Cambridge Examination for Mental Disorders of the Elderly (CAMDEX Section F & H: Medical history) [12], cognition (Mini-Mental State Exam (MMSE) [14], Montreal Cognitive Assessment (MoCA) [16], Clinical Dementia Rating (CDR) [13]), behavior (Neuropsychiatric Inventory (NPI) [18]), mood (Geriatric Depression Scale (GDS) [17], Cornell Scale for Depression in Dementia (CSDD) [20]), and Bristol activities of daily living scale (BADLS) or Alzheimer's Disease Cooperative Study Group – Activities of Daily Living (ADCS-ADL). The Global Deterioration Scale [19] and Telephone Interview of Cognitive Status-Modified (TICS-m) [15] were also used. A lifestyle questionnaire, which covered social contacts, blood pressure, diet, and physical activity information (questionnaires taken from MEDAS and EPIC studies, respectively) was included in the protocol from 2017 [21, 22]. Where it had not been possible to carry out an assessment due to the participant's health prior to death it was often possible to carry out a retrospective interview with the study partner.

The operational criteria for control, mild cognitive impairment, and dementia based on the assessment measures are given in Table 1. As not all participants were able to have all the assessments at each assessment visit (due to fatigue, being unwell, having time constraints, carer responsibilities, for example) the individual measure scores were used in the sequence CDR, MMSE, MoCA, MoCA-blind, Global deterioration scale, and TICS-m with the operational criteria to give cognitive status for the purpose of BDR.

In the case of depression, recognized GDS cut-offs of 0–4, 5–9, and 10+ were used to indicate no depression, mild depression, and severe depression respectively [15], while for CSDD, these were 0–7

(no depression) and 8+(significant depressive symptoms) [16].

Brain donation

Once the participant died, the brain (and spinal cord if consent was in place for that) was removed by the university hospital mortuary. In some cases, a mortuary local to the deceased was used and the brain tissue was then conveyed to the brain bank on ice by a courier approved for the transport of human tissue. A full neuropathological dissection, sampling, and characterization was undertaken according to a standardized BDR protocol by experienced neuropathologists in each of the 5 network brain banks. This protocol, arrived at by consensus across the BDR network and based on the BrainNet Europe initiative [3], generates a narrative description of the regional pathology within the brain together with standardized scoring for Braak tangle pathology [17, 18], Braak Lewy body score [19], Thal phase of A β pathology, Consortium to Establish a Registry of Alzheimer's Disease (CERAD) classification [18], extent, location, and classification of vascular pathology [20], and TDP43 status. This protocol is very similar to that subsequently used by the Medical Research Council (MRC) UK Brain Bank Network for cases of dementia and controls [4]. BDR had a central database to hold neuropathological information that enabled researchers to readily locate samples from BDR donors held in the 5 member brain banks. The MRC UK Brain Bank Network [4] was established shortly after BDR and both organizations worked closely together to ensure, and share best practice. In 2013, the MRC UK Brain Bank Network developed and subsequently populated a searchable database of all brain samples available from UK Brain Banks. Once the MRC UK Brain Bank Network database was fully functioning, the BDR database was 'retired'. BDR cases on the UK Brain Bank Network database are classified according to the hierarchical tree structure based on WHO ICD-10 and researchers can search for individual cases, or groups of cases meeting multiple criteria, for their work.

Blood biobank, GWAS

The funding charities appreciated the addition of blood samples from the BDR cohort would considerably strengthen the usefulness of the clinical data and postmortem brain tissue from participants. Thus, addition of the BDR Blood Biobank, in 2013,

whereby a subgroup of existing BDR participants agreed to blood sample (serum, plasma, buffy coat, DNA, RNA (PAXgene)) collection was a further evolution in cohort value and agility. This subgroup (almost all having no cognitive impairment) was selected by distance of place of residence from the assessment center to adhere to the maximum blood sampling to processing time in the protocol (taken from EU Framework 6 project AddNeuroMed [21]). The standard operating protocol for venepuncture, processing, and storage of blood samples are very similar in all important aspects to that of the National Institute of Health Research Biomedical Research Centre for Mental Health Bioresource, and blood samples are stored at this facility at King's College London. Procedures followed best practice and aimed to provide suitable samples for genetic and biochemical studies.

Another collaborative development with Kevin Morgan at the University of Nottingham has enabled GWAS data to be carried out on most deceased participants, using Whole Exome Sequencing [22] and NeuroChip [23].

How tissue and data is accessed by researchers

Tissue located on the MRC UK Brain Bank and Dementias Platform UK (DPUK; <http://www.dementiasplatform.uk>) databases are accessed via the holding Brain Bank. Applications from *bona fide* researchers for brain tissue and clinical data for dementia research is via a written application form which is considered by the virtual brain bank committees operating under their devolved research ethical committee authority. Applications from outside the UK are reviewed similarly by ethically approved review panels. Data distribution to researchers and applications for blood samples are likewise via Research Ethics Committee devolved ethical authority. However, blood samples will largely be released for research in conjunction with the donated brain tissue. Applicants requesting tissue are required to enter into a Material Transfer Agreement with the universities, where the banks are located, as custodians of the tissue

RESULTS

Recruitment

Of the 3,512 enquiries received by the BDR Coordinating Centre, recruitment enquiries via health

professionals was relatively low, at only 271 (7.7% enquiries). In contrast, national and local media, charities, and the project website, all areas strongly influenced by lay input, were cited by 2,617 (74.5%) enquirers as their information source. First party enquiries numbered 2,553 (72.7%) and 2,663 (75.8%) of all Coordinating Centre enquiries were by potential control participants.

The method of contacting BDR to enquire about taking part was mainly by email or using the website contact form (1,908 or 54.3%), and telephone (1,449, 41.3%). Only 139 (4%) enquiries were by letter, with almost none by other means (14, or 0.4%).

Of the enquiries received, 2,012 (57.3%) were forwarded to the BDR center closest to the participant, and of these 1,176 (58.4%) were recruited into BDR. Enquiries unsuitable for recruitment to BDR (having one or more reasons for exclusion) were often suitable for direct registration with individual brain banks and 965 (27.5%) such enquiries were forwarded to more appropriate donation points. The 535 (15.2%) not recruited or referred to other donation points were from those geographically to remote for brain donation (Northern Ireland, Scottish Highlands and Islands), overseas or the enquiries related to a person already deceased. Many enquiries were received by individual BDR centers but no comparable records were kept so similar analysis could not be undertaken. Recruitment was paused in 2016 at the request of the funders as recruitment targets had been met.

Cohort characteristics

At January 2018, a total of 3,276 volunteers had been recruited to the study, with 3,128 of the recruited 3,276 undergoing baseline assessments and 6,676 follow up assessments undertaken at this census date. Withdrawals by participants prior to death are low, at 144, (4.4% of the recruited cohort). Brain donations have been received from 724 of the 825 deceased participants. While withdrawals are low, lost donations are higher, at 3% of the living cohort but 12.2% of deaths.

Of the recruited cohort, at baseline 77.6% had 11 or more years education (Table 2), greater than that for the general population, which was 47.1% with 11 or more years education. However, both ethnicity and gender were broadly similar for the population over 65. The living cohort at census was predominantly participants recruited without cognitive impairment (71.9%).

Table 2
Comparison of BDR Cohort & General Population: Gender, age, ethnicity, and qualification

	BDR Cohort (n = 3,276)	General population*
Age at Registration		
64 and under [†]	278 (8.5)	3,129,842 (24.0)
65–69	649 (21.7)	3,106,796 (31.4)
70–74	689 (23.0)	2,246,270 (22.7)
75–79	610 (20.3)	1,855,876 (18.7)
80–84	518 (17.3)	1,381,702 (13.9)
85–89	339 (11.3)	836,948 (8.4)
≥90	193 (6.4)	478,217 (4.8)
Female Gender	1962 (59.9)	7,044,693 (54.0)
White Ethnicity (n = 2652)	2622 (98.9)	10,221.5 (95.8) **
No qualifications or ≤10 years of education ^{††}	662 (22.4)	4,880,502 (52.9) ***
Level 1 and above qualifications or ≥11 years of education ^{††}	2298 (77.6)	4,342,571 (47.1) ***

Data for BDR cohort includes living and deceased participants. Data for general population taken from Office for National Statistics, 2011 *Gender & Age structure (E&W). Mid 2013 Population 60+; **Table EE3: Population Estimates by Ethnic Group Rel.8.0; *** Table DC5102EW: Highest level of qualification by sex by age. Level 1:1–4 O Levels/CSE/GCSEs (any grades), Entry Level, Foundation Diploma, NVQ Level 1, Foundation GNVQ, Basic/Essential Skills. [†]not included in proportions for age groups. ^{††}Not all participants supplied education information, n = 2,960.

Almost all (692 of 724) brain donors have assessment data at the date of census and the median interval between assessment and death was 8 months (IQR: 10 months). Based on cognitive scores at the last BDR assessment before death and brain donation, 67.9% (470) had dementia, 3.0% (21) were MCI, and 28.3% (196) had no cognitive impairment. There were a small number (5 or 0.7%) for whom cognition status is inconclusive based on missing or conflicting assessment scores. Also, people recruited who died before being assessed, or recruited close to or at the point of death for whom no assessment was possible have been excluded, accounting for 32 or 1% of the 3,276 consented. with time. The main neuropathological diagnoses and frequencies are given in Table 4, and while BDR was not established as a specialist brain bank for rarer dementias, nonetheless, significant numbers of donations are from participants with rarer dementias.

Furthermore, the level of neuropathological characterization allows researchers to understand the multiple dementia pathologies and cerebrovascular pathologies available. Controls with no neuropathological diagnosis of dementia comprised three

Table 3
Cognitive status at last assessment for deceased and remaining participants

Last Assessment Data Cognitive status	Deceased Participants		Living cohort (2,289) (%)
	(n = 724) (%)	Age at death (y, SD)	
No cognitive impairment	196 (28.3)	85.0 (9.5)	1652 (72.2)
Mild cognitive impairment	21 (3.0)	86.3 (8.4)	184 (8.0)
Dementia	470 (67.9)	82.4 (9.0)	367 (16.0)
Inconclusive	5 (0.7)	84.8 (11.1)	86 (3.8)
No assessment at death	32		
Positive NPI score (any domain)	374 (61.3)		533 (22.8)

Figures do not correspond to the total number of participants as some participants died before an assessment was possible, mostly at the beginning of the project. Some data is not presented but is available within other projects such as OPTIMA- Oxford Project to Investigate Memory and Aging. This data will be captured into the main dataset in the future.

Table 4
Pathology in the deceased

Neuropathological Diagnosis	Frequency	Cumulative Percentage
Control (NIA-AA Low/Not)	148	22
CVD no dementia	17	2.5
ILBD	9	1.3
AD	208	31
LBD	57	8.5
FTLD	34	5.1
VaD	18	2.7
NIA Intermediate	65	9.7
MIX AD DLB	66	9.8
MIX Other	17	2.5
Other	33	4.9
Total	672	100

NIA-AA Low/Not, National Institute on Aging-Alzheimer's Association low or no level of Alzheimer's disease neuropathologic change; AD, Alzheimer's disease; CVD, cerebrovascular disease; ILBD, incidental Lewy body disease; LBD, Lewy body dementias; VaD, vascular dementia; MIX, mixed pathologies; FTLD, frontotemporal lobar dementias; NIA Intermediate, National Institute of Aging-Alzheimer's Association guidelines – intermediate level of Alzheimer's disease neuropathologic change; Other, includes hippocampal sclerosis, agyrophillic grain disease, multiple system atrophy, motor neuron disease, FTLD-FUS, familial tauopathy, Thal45 NIA low, CJD. Neuropathological assessment of 672 of 725 deceased participants was available at time of census.

groups: 1) National Institute of Aging – Alzheimer's Association (NIA-AA) none or low level of AD neuropathologic change ($n = 148$); 2) cerebrovascular disease with no evidence of dementia, ($n = 17$); and 3) incidental Lewy body disease (ILBD) ($n = 9$). Looking just at these three neuropathological control groups as a whole with respect to cognitive status by last assessment before death, 146 (79.3) were cognitively normal, 7 (3.8%) were MCI, 14 (7.6%) had dementia, and 17(9.2%) were not rated by BDR assessment criteria (Table 1). A more detailed analysis of the potential mismatches is underway and will consider other factors, including depression and any other available scores.

By contrast, based on the most recent assessment scores (CDR, MMSE, MoCA, or TICSm), relatively few of the living cohort had MCI or dementia (551 or 24.1%) with the majority having no cognitive impairment (72.2% or 1652) (Table 3). Depression was rated using the GDS or the CSDD (to generate depression criteria for the cohort, not a formal diagnosis of depression). However, over half the living cohort (58%, 1,358) had at least one symptom of depression from the GDS. Assessment of the severity of depression at the last interview for the living participants and the deceased are shown in Table 5. Psychiatric symptoms (as evidenced by a positive NPI score) were present in 22.8% (533).

Data and tissue availability to researchers

Of the 278 tissue requests from universities at census fulfilled by BDR, 3.3% were from Asia and the Middle East, 5.3% from USA and Canada, 9.6% from mainland Europe (32 universities in all), and 81.8% from 28 UK universities. Of the latter, 39.7% of tissue requested went to the BDR universities, however, many were not to researchers within brain banks and many did not have a BDR brain bank collaborator. A brain bank collaborator is not required to access BDR tissue. The last decade has also seen the development and expansion of initiatives to share data across cohorts to speed up research and identify potential participants for clinical studies. DPUK is an overarching initiative that brings together more than 35 existing UK longitudinal cohorts (of which BDR is one) that are ready to be repurposed to accelerate the development of new treatments for dementia [24]. In recognition of the need for high quality clinical data accompanying tissue, some DPUK cohorts are being approached to determine if they would be willing to consider brain donation, whereas this was the original aim for the BDR cohort.

Table 5
Depression data for the living and deceased at most recent assessment

Rating scale		Deceased participants <i>n</i> = 724 (%)	Living cohort <i>n</i> = 2,289 (%)
Geriatric Depression Scale	No depression (0–4)	252 (34.8)	1488 (65)
	Mild/Moderate depression (5–9)	70 (10.9)	175 (7.6)
	Severe depression (10+)	15 (2.1)	29 (1.3)
Cornell Scale for Depression in Dementia	No depression (0–7)	81 (11.2)	96 (4.2)
	Significant depressive symptoms (8+)	45 (6.2)	41 (1.8)

There were 474 cases where there was no assessment of depression at last visit by either CSDD or GDS, of these 65 deceased cases had NPI-D. In some cases, data from previous assessments is available.

The BDR neuropathological data made available via the MRC UK Brain Bank website, in conjunction with the clinical history and summary psychometric data collected during life enables more accurate selection of cases by researchers, including rarer dementias. Where large datasets are required and where access to the full electronic record of all assessment data the DPUK platform represents the best option for researchers.

Furthermore, the GWAS data for 556 BDR brain donors has been made available for research via DPUK. Some cases have been subjected to whole exome sequencing [25], and methylome data will shortly be available for these same cases. These developments will allow for the first time, triangulation of clinical, neuropathological, genetic, and epigenetic data for a large cohort.

A subset of the cohort (just over 400 controls) has consented to blood sampling (serum, plasma, DNA, RNA); however, the funders (AS and ARUK) currently consider these samples have maximal value as linked samples, so, apart from genetic analysis these samples will most likely be retained for use with brain tissue and clinical data once the participant dies.

DISCUSSION

The importance and value of planned brain donation from potentially highly informative cohorts is widely recognized [8–10]. Testament to the success of BDR was the speed of recruitment and the large number of donations received from well characterized cognitively normal individuals. BDR was funded as a ‘stand-alone’ project of well characterized participants coming to brain donation and has frequently reviewed its position within the wider basic and clinical research environment. The value of the cohort has been increased by adapting to the current clinical and research landscapes. Moreover, as the majority of

participants are still living and contributing assessment data (and, for some, blood samples) the value of the cohort will continue to grow.

This initiative was set in motion by people with dementia and their families and this is reflected in their high level of involvement at all stages of the project [12]. It is recognized that public patient involvement (PPI) is difficult in dementia research due to progressive cognitive impairment and hence families of people with dementia are often the closest approximation to patient involvement. BDR is important to participants and their families as a way of contributing to dementia research whether or not they have dementia.

As a network, BDR operates as one with respect to how assessment data is collected and tissue is processed, classified and stored through the adoption of standard operating procedures across all centers. BDR is an important and expanding source of control cases for dementia research, the controls are very well characterized by assessment data and by neuropathology.

Most of the brain donations thus far received have genetic information and will soon have epigenetic and methylation data. This, together with computing power and analysis pipelines available for data analysis at scale through DPUK, represent significant resource to dementia researchers. Tissue and data are freely available to all bona fide researchers, subject only to an ethically approved request process and cost recovery. Case selection and tissue access has become very straightforward with the MRC UK Brain Bank Network database and DPUK platform.

Having been based on the AddNeuroMed project [14], the assessment protocol was set up to encompass measures in wide usage to maximize the overlap with as many other studies as possible [14]. As an observational study, BDR does not prohibit involvement in clinical trials, a factor that has undoubtedly enhanced retention. Participants are asked for consent

to receive other relevant study information. This has enabled BDR to integrate well with relevant initiatives such as DPUK, and readiness cohorts; EPAD, Join Dementia Research and DPUK trial readiness cohorts. Thus far BDR participants have been able to take part in TOMMORROW, and the PROTECT study [26], for example.

BDR recruitment was wider than the memory clinic context, aimed at attracting those without dementia to the cohort. Driving this was active participation of lay representatives. Involvement of lay representatives with experience of dementia from the target recruitment age group, brought an element of 'peer to peer' communication in recruitment material content, project communications and recruitment activity, which in our view, enhanced accessibility of project information [12]. The lay input, charity input and charity contact network most certainly opened community access opportunities in a way that would not have been possible for the BDR staff team working alone. Largely due to the funding charities and lay input, recruitment to BDR was faster than initially envisaged, with the greatest success being the proportion of participants without a diagnosis of dementia. Despite the longer life expectancy for those without dementia, a large number of brain donations have already been received from well characterized cognitively normal individuals, which has had a significant impact on the availability of high quality control tissue for research. The experience of BDR is that people without dementia are very willing to take part as controls and donate their brains once the importance of such donations are appreciated. BDR is still receiving many enquiries although all advertising has ceased and where possible these enquiries are signposted to other suitable projects with the agreement of our Ethics committee.

Limitations

As with any cohort study, there are limitations. Firstly the BDR cohort is self-selecting. In keeping with many observational cohorts, participants are mostly from less socially and economically deprived areas (so introducing biases toward higher educational achievement and white ethnicity). Although the use of consultees and study partners facilitates inclusion of participants with dementia, inevitably the sample is subject to healthy volunteer bias.

Secondly participants do not have a formal clinical diagnosis, but self-report clinical diagnosis at registration, and while the protocol includes

cognitive and neuropathological assessment, confirmation of participant diagnostic status during life through the hospital clinic setting would enhance data quality. It is a strength of the BDR cohort that persons with and without memory impairment and with and without comorbidities were recruited, resulting in significant numbers of brain donations from individuals with rarer dementias and the entire cohort being more representative in terms of comorbidities associated with old age [27].

By comparison, the Cognitive Function and Aging Study (CFAS, <http://www.cfas.ac.uk/>), a population based data study found non-participation increased substantially in the two decade interval between CFAS I and CFAS II, although for both, individuals living in areas of greater social deprivation were more likely to not take part [28]. However, population-based studies may also be subject to the same bias in respect of brain donation because brain donation is often restricted to certain types of participants. In CFAS, only the most intensively studied participants were approached about brain donation, of which a subset individuals gave consent [29], so it is, as yet, unclear to what extent the subset consenting to brain donation still reflects the wider population.

Thirdly the absence of imaging data or cerebrospinal fluid sample collection could also be considered study weaknesses. However, some participants have this data available having previously been part of another cohort undertaking this. Fourthly, there is a need to balance assessment burden of detailed psychometric testing with maximizing cohort retention, hence not every assessment desirable in a longitudinal cohort study can be present in any single cohort.

Strengths

Ancillary strengths include excellent retention and participant satisfaction [13] and electronic collection and storage of all data. A core aim of BDR was to facilitate and promote dementia research and the many tissue requests and growing number of data requests, (almost 300 to census resulting in 200 publications) affirm this.

Combining longitudinal data collection and brain donation provides the unique opportunity to explore the relationship between life factors, genetics, epigenetics, and histopathological and biochemical indices at postmortem.

Study partners and nominated representatives are recognized to be of prime importance to

maintaining the cohort and receiving brain donations at death. Work to consider their needs, stresses, and motivators is ongoing.

BDR addresses the urgent need to increase the supply of highly characterized healthy brain tissue, with protocols standardized across the BDR network, but also offers an opportunity to capture and to monitor the early signs of cognitive decline. With the surviving cohort comprising over 75% dementia free volunteer donors, there is greater likelihood of collecting valuable brain tissue from those dying without dementia or at an earlier stage in the dementia process, through deaths due to other unrelated causes. Extensive clinical and neuropathological data, together with the results of genetic and epigenetic analysis across multiple brain regions (forthcoming) are freely available and searchable through web-based platforms (e.g., DPUK, MRC UKBBN).

Driven by the funders' (AS and ARUK) desire to accelerate and expand research into dementias, BDR was set up utilizing assessment that maximized the ability of the data collected to fit with that of other studies. The concept and value of 'big data' to study populations for smaller genetic and environmental effects in dementia has gathered momentum and BDR remains committed to staying centrally placed in this developing research and clinical trial environment, whilst fulfilling its aim of facilitating research by tissue and data provision from highly characterized donors.

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